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(71) Applicant and
(72) Inventor: SLOVICK, David, Ian [GB/GB]; 6 The Ridgeway, Westcliff on Sea, Essex SS0 8NT (GB).

(74) Agent: MESSULAM, Alec, Moses; A. Messulam & Co. Ltd., 43-45 High Road, Bushey Heath, Bushey, Hertfordshire WD23 1EE (GB).

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(54) Title: METHOD OF DISPENSING PHARMACEUTICAL SUBSTANCES

(57) Abstract: A device is disclosed for filling a set of capsules with microspheres containing active substances to permit the dosage of each individual active substance in each capsule of the set to be varied to suit the requirements of an individual patient. The device comprises a plurality of loading stations each receiving a canister filled with micro-spheres containing a predetermined quantity of a respective one of the active substances. A programmable metering unit associated with the loading stations meters programmed numbers of microspheres from the individual canisters, and the counted micro-spheres are introduced into the individual capsules of the set.

METHOD OF DISPENSING PHARMACEUTICAL SUBSTANCES

Field of the invention

The present invention relates to the field of dispensing pharmaceutical formulations.

Background of the invention

Medicinal dosage forms (such as tablets or capsules) contain an active substance present in micro– or milli– gram amounts combined with inactive substances which promote physical or chemical stability, ease of handling and identification of the product.

Current European guidance prefers that tablets be sold in 'original dispensing packs' consisting of a metal foil laminated onto a plastic 'blister' sheet, containing a one month supply of individual tablets, affording a useful shelf life.

Patients with serious conditions such as ischaemic heart disease or congestive heart failure are required to take daily a large number of medications, which frequently results in a failure to comply accurately with the recommended prescription. This can be due to:

- forgetting pills
- confusion with dosing schedules
- unwillingness or fear of consuming large numbers of pills
- errors in taking medications resulting in running out of some pills before others.

A formal study has shown patients 'encash' prescriptions given by medical practitioners at local pharmacies for approximately 60% of the calculated total necessary number of pills, when given a regular prescription

of one single tablet daily. When the prescription is for two pills daily, the encashment rate can fall to only 15%. Taking a sub-optimal number of pills would adversely affect quality of life and also reduce survival prognosis, since many treatments are life-extending, particularly when used in combination.

To mitigate this problem, it has previously been suggested that blister packing be offered as a free service by dispensing pharmacists, putting a number of tablets together in a day-coded package. However, patients are still faced with the same large number of tablets to take, which discourages them from taking their treatment reliably. Blister packing is currently performed by only a few dispensing pharmacists as a special service, and is not widely available.

It has further been proposed to manufacture tablets containing fixed dose combinations of two or more active substances. This proposal suffers from the disadvantage that fixed dose combination tablets (typically of two active substances) are recommended only for patients who have previously been stabilised on the individual components. Any particular fixed dose combination made by a manufacturer might be unsuitable or harmful for some patients, by causing metabolic disturbances or excessive or inadequate effects.

Object of the invention

The present invention therefore seeks to reduce the total number of dose forms ('pills') that patients are required to take daily.

Summary of the invention

In its broadest aspect, the present invention provides a device for filling a set of capsules with microspheres

containing active substances to permit the dosage of each individual active substance in each capsule of the set to be varied to suit the requirements of an individual patient, which device comprises a plurality of loading stations each receiving a canister filled with micro-spheres containing a predetermined quantity of a respective one of the active substances, a programmable metering unit associated with the loading stations for metering programmed numbers of microspheres from the individual canisters, and means for introducing the counted micro-spheres into the individual capsules of the set.

The invention thus provides a dispensing pharmacist with the facility to mix in one capsule a combination of different active substances in absolute and relative amounts that are specifically prescribed for the patient by a medical practitioner. Not only can the doses and relative amounts of the active substances be tailored to individual patient requirements in any one set, but the different capsules within a set may contain different doses from one another, enabling a particular drug to be phased in or out over the period during which the capsules of the set are to be taken by the patient. This is referred to as titration.

Preferably, such capsules should be prepared and packed in an easily available pack for patients locally in community or hospital pharmacies.

It is important for a medical practitioner or a pharmacist to be able to ascertain the medication previously taken by a patient.

With this aim in mind, it is possible for the capsules, or their packaging if they are blister packed, to be marked with a code that permits the contained active substances and their dosage to be determined.

It is preferred that the canisters should be shaped externally to provide secure mounting onto the device in a predetermined orientation and that their internal shape be such as to ensure accurate delivery of micro-spheres under gravity.

Conveniently, the canisters may be formed in two parts that seal hermetically against each other to prevent entry of water vapour or to contain a preservative gas introduced into the canisters. Such sealing of the canisters is also advantageous in that it prevents tampering.

To comply with best practice, the filled capsules may additionally be sealed into an 'original pack' for dispensing to patients.

In order to meter the correct number of micro-spheres from a supply canister into an individual capsule, it is possible to use as a programmable counter a reciprocating perforated plate, or an indented wheel, controlled by an indexing stepping mechanism. As an alternative, individual microspheres may be counted optically (by interruption of a light beam) and the flow of microspheres into a capsule may be stopped when the desired number has been reached.

For proper identification of the capsules, each capsule or more preferably the blister pack containing several capsules may be suitably encoded, for example by means of a bar code or colour coding. The encoded data may be used to identify the dispensing pharmacy, to identify the contained medications, using information stored in a database in the pharmacy.

It is not essential that the code uniquely identify the contained medications and their dosages. As the dispensing pharmacy is identified, it suffices for the pharmacy to maintain a register giving more details about the

medications and conveniently such data could be accessed directly by medical practitioners and hospitals by using the Internet. Alternatively, the information could be held centrally, allowing access by approved individuals in a secure manner.

As the capsule or dispensing pack codes need not carry individual patient details, confidentiality is preserved.

The range of active substances to be formulated in microspheres is potentially wide, but would be most appropriate where the typical dose ranged from micrograms to tens of milligrams.

The external design of the manufacturers' supply canisters for the microspheres may preferably be of standardised dimensions and mechanisms for sealing/unsealing and encoding so as to ensure secure mounting into the capsule filling device and to allow positive identification of the contents of the canister through a mechanical/electrical/radio/magnetic signalling system adopting a standard code.

The internal design characteristics of the manufacturers' supply canister for the microspheres may be variable to permit adjustment of storage conditions for an adequate shelf life for the individual active substances. For example, the canisters may be filled with an inert gas, masked against entry of light, or coated to prevent water vapour entry.

The external design of the microsphere supply canisters may suitably incorporate a standardised space for labelling giving visual identification and details of contents.

Conveniently, the capsule filling device may be controlled by a computer installation that includes a

printer and the computer may be programmed to print labels that give details of the dispensing pharmacy, patient name, active substance, manufacturer, expiry date and manufacturers' product codes. Such labels may be self adhesive and prepared for attachment to the original dispensing pack and to the outside of a cardboard box containing treatment supply for a 28 or 30 day period.

The original dispensing pack containing the individually filled capsules should preferably identify capsules for individual days of the week for ease of treatment compliance. Such packs may also conform to standardised dimensions and carry protrusions and/or perforations for engagement with the mechanism of an optional additional device for the extraction of the capsules from the original dispensing pack at the patients home.

Two types of extracting device such as described immediately above may be envisaged. The first may be fully automatic, containing original treatment pack for one month's supply of capsules, with ability to present the dose form to the patient at a preset time with audible tone/voice recording/visual alert. The second may be a semi-automatic device for easy removal of the capsule from the original dispensing pack, aiding patients with low sight, reduced manual dexterity or poor memory (prompted by magnifying lens window to view day of the week on the contained original dispensing pack).

The individual components for implementation of the invention may comprise pre-manufactured pharmaceutical capsules which are separated into component halves. The lower-parts may be inserted vertically into strips or wheels which hold twenty eight or fifty six half capsules arranged around the margin of the strip or wheel. The wheel or strip is capable of precision mounting into the capsule-filling

device to allow precise filling of capsules with microspheres. A matching strip or wheel is provided to contain pre-inserted matching top-halves of the capsules. Batch closure of filled capsules is effected by application of opposing strips or wheels containing capsule upper and lower halves.

The capsule halves may be of different colours (e.g. red, orange, yellow, green, light blue, dark blue, brown, black, white, transparent, and they may have superimposed contrasting colour band(s). In this manner, colour coding may be achieved to allow the origin of the capsules to be identified. Alphanumeric codes may alternatively or additionally be pre-printed onto one half of capsule (e.g. 10 characters) and such codes may be standardised to enable national identification.

The microsphere canister will typically contain sufficient spheres for various doses for multiples of twenty eight capsules. Asymmetric shape can be used to ensure standard orientation into the capsule filling device. Labels printed onto the canister can be encoded to allow automatic transfer of details of manufacturer, active substance, dose, batch, product licence number and expiry date. The canister is sealed until insertion into the capsule filling device for security against loss of microsphere or contamination of contents.

The capsule filling device should be able to carry plastic strips or wheels containing 28 or 30 capsules and to allow mounting of up to ten manufacturers' canisters of microspheres. The filling device is microprocessor controlled for accurate dispensing of appropriate numbers of each type of microsphere into each capsule in turn. The microprocessor of the filling device should preferably be able to interface with a pharmacy computer to allow transfer of prescribing information without re-keying of prescription

data to the device, and despatching of securely encoded data to distant secure database via internet connection from the device, via the pharmacy computer. The filling device may also be designed to allow future prescription data entry by barcode read directly off prescription form via the pharmacy computer or downloaded from medical practitioners' systems.

As equipment for counting microspheres is already known, for example from FR 2689092, and as equipment for filling and sealing capsules is also already known per se, for example from US 4615165, it is believed that the mechanical construction of equipment suitable for implementing the invention will be clear to the person skilled in the art without the need for further detailed description.

The invention resides not in the construction of any one of the necessary components but in the provision of a device that affords the pharmacist the flexibility to tailor the composition of the active substances in a set of capsules to the needs of an individual patient, as prescribed by a medical practitioner. In this way, a patient need only swallow one capsule at any one time, thereby ensuring that the patient adheres to the regime specified by the practitioner.

CLAIMS

1. A device for filling a set of capsules with microspheres containing active substances to permit the dosage of each individual active substance in each capsule of the set to be varied to suit the requirements of an individual patient, which device comprises a plurality of loading stations each receiving a canister filled with micro-spheres containing a predetermined quantity of a respective one of the active substances, a programmable metering unit associated with the loading stations for metering programmed numbers of microspheres from the individual canisters, and means for introducing the counted micro-spheres into the individual capsules of the set.

2. A device as claimed in claim 1, wherein the device comprises means for separating the two parts of each capsule from one another and combining them after the lower part of the capsule has been filed.

3. A device as claimed in claim 1 or 2, wherein the metering unit is a counter that includes a reciprocating perforated plate, or an indented wheel, controlled by an indexing stepping mechanism.

4. A device as claimed in any preceding claim, wherein the loading stations have means for identifying the contents of a canister received therein from coding on the canister.

INTERNATIONAL SEARCH REPORT

Interna nal Application No
PCT/GB 02/04631

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61J3/07

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61J A61K B65B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 199 51 504 A (ESPE DENTAL AG) 10 May 2001 (2001-05-10) the whole document	1,4
X Y	EP 0 587 085 A (IHDE STEFAN KLAUS ALFRED) 16 March 1994 (1994-03-16) page 6, line 49 -page 8, line 43; figures 1,5	1 2-4
Y	US 4 615 165 A (GAMBERINI ERNESTO) 7 October 1986 (1986-10-07) cited in the application the whole document	2
Y	FR 2 689 092 A (BOIRON) 1 October 1993 (1993-10-01) cited in the application the whole document	3

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 January 2003	30/01/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Baert, F

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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